REMARKS

Claims 16-29 and 31-44 are pending and stand rejected in the final Office action issued June 18, 2003. There are two outstanding rejections to these claims under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a). These rejections are addressed below.

Rejection of Claims for Alleged Indefiniteness

Claims 16-29 and 31-44 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed. As shown in the amendment filed January 2, 2003, the meaning of "indirect causes" is clearly understood by the person of ordinary skill in the art. For example, the specification clearly distinguished indirect causes from direct causes by providing examples of indirect causes on page 31, line 31 to page 32, line 5: "The indirect causes are classified into the sepsis syndrome severe non-thoracic trauma, hypertransfusion during emergency resuscitation, and an artificial cardial pulmonary bypass surgery." These show by example types of indirect conditions that lead to hypoxemia in acute lung injury, and the person of ordinary skill in the art understood the scope of other indirect causes that were applicable. Thus, the specification clearly shows multiple examples of indirect causes were known to persons of ordinary skill in the art and therefore the meets and bounds of the claims were clearly delineated.

The Office alleged in the action dated June 18, 2003 that limitations from the specification cannot be read into the claims and there are many indirect causes which may or may not be intended within the meets and bounds of the claimed subject matter. The applicability of this position is not understood. Specifically, the portions of this specification noted in the amendment filed January 2, 2003 and this response are featured to show that the person of ordinary skill in the art understood the meets and bounds of the term "indirect causes" and were not featured to read limitations into the claims. Thus, the listing of multiple indirect causes that lead to hypoxemia in acute lung injury are indicative that the person of ordinary skill in the art understood the meets and bounds of the term. Accordingly, it is respectfully requested the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn in view of the clear meaning of the term "indirect causes".

Rejection of Claims for Allegedly Obviousness

Claims 16-29 and 31-44 were again rejected under 35 U.S.C. § 103(a) as allegedly being unpatenable over Folkesson *et al.* in view of Slotman. The Office cites Slotman for the alleged teaching that IL-8 was known as an inflammatory mediator of hypoxemia in acute lung injury resulting from indirect causes. The Office cites Folkesson for the alleged teaching that IL-8 was critical for the development of lung injury and that neutralization of IL-8 provided a therapeutic treatment for acute lung injury. The rejection is respectfully traversed. The cited combination does not teach or suggest that IL-8 should be targeted for treating hypoxemia in acute lung injury resulting from indirect causes, and provides no reasonable expectation of success for doing so.

The applicants stress here that the combination of Folkesson and Slotman do not teach or suggest the claimed methods for hypoxemia. As noted in previous amendments, Folkesson is limited only to lung injury caused by acid inhalation, which is a direct cause of lung injury and not an indirect cause of lung injury as claimed. Slotman is limited to disclosures of "adult respiratory distress syndrome" and "septic shock." These conditions are distinct from the claimed condition of "hypoxemia." To clarify this distinction, enclosed are copies of sections from *Review of Medical Physiology,* specifically pages 594-595 and pages 636-648. Adult respiratory distress syndrome is described on page 594, right column, third paragraph and septic shock is described on page 95, left column, lines 4-10. None of these descriptions mention hypoxemia, and therefore, the cited combination does not teach or suggest the claimed methods of treating hypoxemia in acute lung injury. Thus, no *prima facie* case of obviousness is established by the cited combination.

The amendment filed January 2, 2003 also clarified other reasons why the cited combination cannot support a *prima facie* case of obviousness. The amendment made clear that Folkesson was limited only to lung injury caused by acid inhalation, which is a direct cause. Slotman disclosed no treatment methods and provided no teaching or suggestion as to which cell mediators lead to the inflammatory conditions discussed therein. While Slotman mentioned IL-8 in a list of more than seventeen (17) potential causative of agents of certain systemic inflammatory conditions, the disclosure does not teach or suggest IL-8 alone as a target for treating hypoxemia in acute lung injury resulting by indirect causes. Specifically, there is nothing in Slotman or Folkesson suggesting that one skilled in the art should specifically target IL-8 for the treatment of hypoxemia

in lung injury resulting from indirect causes and not the other potential causative agents listed in Slotman. There is nothing in the Slotman disclosure that teaches or suggest one of ordinary skill in the art would pick IL-8 out of the long list of other molecules that allegedly cause inflammatory conditions. Folkesson does not provide the motivation to choose IL-8 from the list because it is limited to treating lung injury resulting from direct causes, which is a distinct condition from lung injury resulting from indirect causes, as discussed in detail herein and in the amendment filed January 2, 2003. Thus, a person of ordinary skill in the art would not have chosen IL-8 as a causative agent of hypoxemia from the combination of Slotman and Folkesson and would not have arrived at the claimed subject matter.

Thus, the combination of Folkesson and Slotman provided no guidance or suggestion for targeting IL-8 as the causative agent of hypoxemia in acute lung injury resulting from indirect causes, and therefore the claimed subject matter is inventive and not obvious. The Office alleges that Folkesson teaches the active ingredient, an IL-8 antibody, and that Slotman allegedly teaches that IL-8 is involved in a wide variety of indirect or direct inflammatory diseases. However, as noted above, IL-8 is camouflaged among a large number of potential causative agents in Slotman and a person of ordinary skill in the art would not have known that an IL-8 antibody should be applied for the treatment of hypoxemia in indirectly caused lung injuries.

The Office also argues that this "specific indirect diseases applicants argue are not an absolute requirement of the claims." This position is not understood. The claims clearly specify that the acute lung injury results from indirect causes (see e.g., claim 31), and therefore the claims are clearly directed to methods for treating lung injury resulting from indirect causes. Accordingly, the claim language clearly distinguishes the treatment of hypoxemia and lung injury resulting from indirect causes from the treatment method discussed in Folkesson. As Slotman did not lead the person of ordinary skill in the art to apply the anti IL-8 antibody discussed in Folkesson to the treatment of hypoxemia and acute lung injury resulting from an indirect cause, the cited combination cannot support a *prima facie* case of obviousness.

Underscoring the claimed limitation to indirectly caused lung injury, the amendment filed January 2, 2003 explained that a treatment efficacious for lung injury resulting from direct causes sometimes is inapplicable to indirectly caused lung injuries. Thus, specifying that the claims are directed to treating hypoxemia in lung injury resulting from indirect causes is important since

not all treatments of lung injury resulting from direct causes are applicable to treating lung injury resulting from indirect causes. As the methods described in Folkesson apply only to lung injury resulting from direct causes and Slotman fails to show that IL-8 alone specifically can be targeted to treat hypoxemia in lung injury resulting from indirect causes, there was no reasonable expectation for successfully practicing the methods claimed herein. Accordingly, it is respectfully requested that the Office withdraw the rejection of the pending claims.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or fees due in connection with this document to **Deposit Account No. 03-1952** referencing docket no. 350292000500 However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By _____

Bruce D. Grant
Registration No.: 47,608
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-7962

a LANGE medical book

Review of Medical Physiology

eighteenth edition

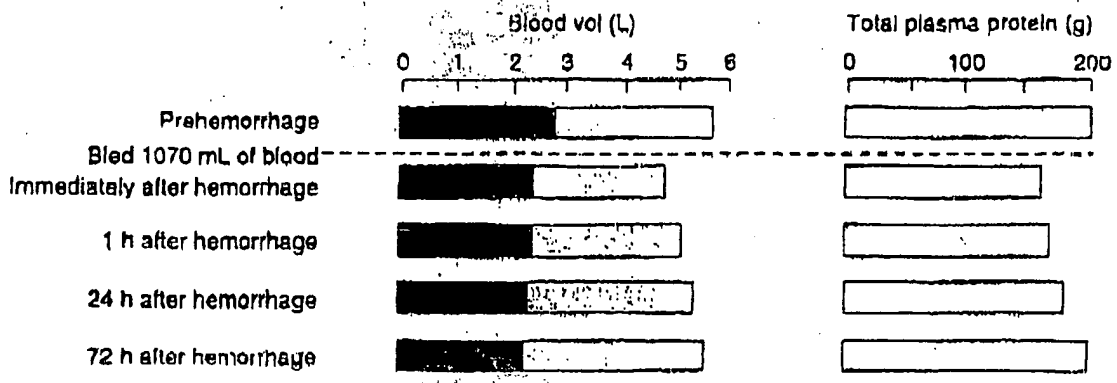


Figure 33–6. Changes in red cell volume (dark color), plasma volume (light color), and total plasma protein following hemorrhage in a normal human subject. (From data in Keele CA, Neil E: *Samson Wright's Applied Physiology*, 11th ed. Oxford Univ Press, 1965.)

7.5 g/dL. Weakness becomes appreciable at about 6 g/dL; dyspnea at rest appears at about 3 g/dL; and the heart fails when the hemoglobin level falls to 2 g/dL.

Refractory Shock

Depending largely upon the amount of blood lost, some patients die soon after hemorrhage and others recover as the compensatory mechanisms, aided by appropriate treatment, gradually restore the circulation to normal. In an intermediate group of patients, shock persists for hours and gradually progresses to a state in which there is no longer any response to vasopressor drugs and in which, even if the blood volume is returned to normal, cardiac output remains depressed. This is known as **refractory shock.** The condition is not unique to hemorrhagic shock but occurs in other forms as well. It used to be called **irreversible shock,** and patients still do die despite vigorous treatment. However, more and more patients are saved as understanding of the pathophysiologic mechanisms increases and treatment is improved. Therefore, refractory shock seems to be a more appropriate term.

Spasm of the precapillary sphincters and venules, especially in the splanchnic region, is a prominent feature at this stage. The reduced capillary perfusion due to the constriction of the precapillary sphincters leads to hypoxic tissue damage. After 3–5 hours, the precapillary sphinchters dilate while the venules remain constricted. Blood now enters the capillaries but stagnates in these vessels, so that the tissue hypoxia continues. Capillary hydrostatic pressure rises, and fluid leaves the vascular system in increasing amounts. Granulocytes adhere to the injured vessel walls and release free radicals, especially O_2^-, and this causes further tissue damage. An antibody to the protein complex that binds neutrophils to tissue has been reported to improve survival in severe shock. There is evidence that damage to the gastrointestinal mucosa permits entry of bacteria into the circulation.

Various positive feedback mechanisms contribute to the production of refractory shock. For example, severe cerebral ischemia leads eventually to depression of the vasomotor and cardiac areas of the brain, causing vasodilation and reduction of the heart rate. These both make the blood pressure drop further, with a further reduction in cerebral blood flow and further depression of the vasomotor and cardiac areas.

Another important example of this type of positive feedback is myocardial depression. In severe shock, the coronary blood flow is reduced because of the hypotension and tachycardia (see Chapter 32), even though the coronary vessels are dilated. The myocardial failure makes the shock and the acidosis worse, and this in turn leads to further depression of myocardial function. If the reduction is marked and prolonged, the myocardium may be damaged to the point where cardiac output cannot be restored to normal in spite of reexpansion of the blood volume.

A late complication of shock that can be fatal is pulmonary damage with the production of **acute respiratory distress syndrome (ARDS, adult respiratory distress syndrome;** see Chapter 37). This syndrome is characterized by acute respiratory failure with a high mortality, and it can be triggered not only by shock but also by sepsis, lung contusion, other forms of trauma, and other serious conditions. The common feature seems to be damage to capillary endothelial cells and alveolar epithelial cells, with release of cytokines.

Other Forms of Hypovolemic Shock

Traumatic shock develops when there is severe damage to muscle and bone. This is the type of shock seen in battle casualties and automobile accident victims. Frank bleeding into the injured areas is the principal cause of the shock, although some plasma also enters the tissue. The amount of blood which can be lost into an injury that appears relatively minor is remarkable; the thigh muscles can accommodate 1 L of extravasated blood, for example, with an increase in the diameter of the thigh of only 1 cm.

Breakdown of skeletal muscle (**rhabdomyolysis**) is a serious additional problem when shock is accompanied by extensive muscle crushing (**crush syndrome**). When pressure on the tissues is relieved and they are once again perfused with blood, free radicals are generated, and these cause further tissue destruction (**reperfusion-induced injury**). Many of the free radicals are generated because during ischemia, tissue xanthine dehydrogenase is converted to xanthine oxidase, and when perfusion is restored, this enzyme generates O_2^-. Adherent white blood cells in the tissues also generate free radicals. The xanthine oxidase inhibitor allopurinol and antibodies that prevent neutrophil adhesion reduce the severity of reperfusion injury. An additional cause of tissue damage in reperfused areas is marked intracellular Ca^{2+} excess, which is presumably due to exchange of excess intracellular Na^+ in damaged tissues for extracellular Ca^{2+}. Kidney damage is also common in the crush syndrome. It is due to accumulation of myoglobin and other products from reperfused tissue in kidneys in which glomerular filtration is already reduced by shock. The products damage and clog the tubules, frequently causing anuria, which may be fatal.

Surgical shock is due to the combination in various proportions of external hemorrhage, bleeding into injured tissues, and dehydration.

In **burn shock**, the most apparent abnormality is loss of plasma as exudate from the burned surfaces. Since the loss in this situation is plasma rather than whole blood, the hematocrit rises and **hemoconcentration** is a prominent finding. Burns also cause complex, poorly understood metabolic changes in addition to fluid loss. For example, there is a 50% rise in metabolic rate of nonthyroidal origin, and some burned patients develop hemolytic anemia. Because of these complications, plus the severity of the shock and the problems of sepsis and kidney damage, the mortality rate when third-degree burns cover more than 75% of the body is still close to 100%.

Hypovolemic shock is a complication of various metabolic and infectious diseases. For example, although the mechanism is different in each case, adrenal insufficiency, diabetic ketoacidosis, and severe diarrhea are all characterized by loss of Na^+ from the circulation. The resultant decline in plasma volume may be severe enough to precipitate cardiovascular collapse.

Distributive Shock

As noted above, distributive shock occurs when the blood volume is normal but the capacity of the circulation is increased by marked vasodilation. It is also called "warm shock" because the skin is not cold and clammy, as it is in hypovolemic shock. A good example is **anaphylactic shock**, a rapidly developing, severe allergic reaction that sometimes occurs when an individual who has previously been sensitized to an antigen is reexposed to it. The resultant antigen-antibody reaction releases large quantities of histamine, causing increased capillary permeability and widespread dilation of arterioles and capillaries.

Another common form of distributive shock is **septic shock**. In this condition, bacterial toxins cause vasodilation. In addition, sepsis depresses the myocardium and increases capillary permeability, so that plasma leaks into the tissues and blood volume falls. Consequently, septic shock is cardiogenic and hypovolemic as well as distributive.

In febrile patients, shock is likely to be more severe because the cutaneous blood vessels are often dilated (see Chapter 32), increasing the disparity between the capacity of the vascular system and the available circulating blood volume.

The gram-negative bacteria that often cause septic shock release **endotoxin**, the cell wall lipopolysaccharide of the organisms. It causes macrophages to produce increased amounts of cytokines. Antibodies against the cytokines or portions of the endotoxin molecule may be of some value in treating septic shock, but results in large clinical trials have been disappointing. Glucocorticoids are of value in animals but not in humans.

A third type of distributive shock is **neurogenic shock**, in which sudden autonomic activity results in vasodilation and pooling of blood in the veins. Examples include fainting in response to strong emotion such as overwhelming fear or grief.

Fainting

Fainting, or **syncope**, is sudden, transient loss of consciousness. It can be due to metabolic or neurologic abnormalities, but more commonly it is due to peripheral vascular or cardiac abnormalities that cause inadequate cerebral blood flow. It is often benign and is most commonly due to abrupt vasodilation. This produces hypotension, generally in association with bradycardia. The term **vasovagal syncope** has been coined to denote this entity. **Postural syncope** is fainting due to pooling of blood in the dependent parts of the body on standing. **Micturition syncope**, fainting during urination, occurs in patients with orthostatic hypotension. It is due to the combination of the orthostasis and reflex bradycardia induced by voiding in these patients. Pressure on the carotid sinus, produced, for example, by a tight collar, can cause such marked bradycardia and vasodilation that fainting results (**carotid sinus syncope**). Rarely, vasodilation and bradycardia may be precipitated by swallowing (**deglutition syncope**). **Cough syncope** occurs when the increase in intrathoracic pressure during straining or coughing is sufficient to block venous return. **Effort syncope** is fainting on exertion as a result of inability to increase cardiac output to meet the increased demands of the tissues and is particularly common in patients with aortic or pulmonary stenosis.

Syncope can also be due to more serious abnormalities. About 25% of syncopal episodes are of cardiac

tion produced by the acidosis is dependent on the carotid bodies and does not occur if they are removed.

The respiratory rate after exercise does not reach basal levels until the O_2 debt is repaid. This may take as long as 90 minutes. The stimulus to ventilation after exercise is not the arterial P_{CO_2}, which is normal or low, or the arterial P_{O_2}, which is normal or high, but the elevated arterial H^+ concentration due to the lactic acidemia. The magnitude of the O_2 debt is the amount by which O_2 consumption exceeds basal consumption from the end of exertion until the O_2 consumption has returned to preexercise basal levels. During repayment of the O_2 debt, there is a small rise in the O_2 concentration in muscle myoglobin. ATP and phosphorylcreatine are resynthesized, and lactic acid is removed. Eighty percent of the lactic acid is converted to glycogen and 20% is metabolized to CO_2 and H_2O.

Because of the extra CO_2 produced by the buffering of lactic acid during strenous exercise, the R rises, reaching 1.5–2.0. After exertion, while the O_2 debt is being repaid, the R falls to 0.5 or less.

Changes in the Tissues

Maximum O_2 uptake during exercise is limited by the maximum rate at which O_2 is transported to the mitochondria in the exercising muscle. However, this limitation is not normally due to deficient O_2 uptake in the lungs, and hemoglobin in arterial blood is saturated even during the most severe exercise.

During exercise, the contracting muscles use more O_2, and the tissue P_{O_2} and the P_{O_2} in venous blood from exercising muscle fall nearly to zero. More O_2 diffuses from the blood, the blood P_{O_2} of the blood in the muscles drops, and more O_2 is removed from hemoglobin. Because the capillary bed of contracting muscle is dilated and many previously closed capillaries are open, the mean distance from the blood to the tissue cells is greatly decreased; this facilitates the movement of O_2 from blood to cells. The oxygen-hemoglobin dissociation curve is steep in the P_{O_2} range below 60 mm Hg, and a relatively large amount of O_2 is supplied for each drop of 1 mm Hg in P_{O_2} (see Fig 35–2). Additional O_2 is supplied because, as a result of the accumulation of CO_2 and the rise in temperature in active tissues—and perhaps because of a rise in red blood cell 2,3-DPG—the dissociation curve shifts to the right (see Fig 35–3). The net effect is a threefold increase in O_2 extraction from each unit of blood. Since this increase is accompanied by a 30-fold or greater increase in blood flow, it permits the metabolic rate of muscle to rise as much as 100-fold during exercise (see Chapter 3).

Fatigue

Fatigue is a poorly understood phenomenon that is a normal consequence of intense exercise or mental effort. In addition, it is a symptom of many different diseases. During exercise, acidosis and other factors contribute to its production. The subjective hardness or "heaviness" of exercise correlates with the rate of O_2 consumption, not with the actual work performed in kg-m/min. Barrages of impulses in afferents from proprioceptors in muscles are said to make one feel "tired." The effects of the acidosis on the brain may contribute to the sensation of fatigue. Prolonged exercise produces hypoglycemia in normal individuals, but prevention of the hypoglycemia does not affect endurance or delay the onset of exhaustion. On the other hand, there is a correlation in humans between exhaustion and the degree of depletion of muscle glycogen, as determined by muscle biopsy. Sustained muscle contractions are painful, because the muscle becomes ischemic and a substance that stimulates pain endings accumulates ("P factor"; see Chapter 7). However, intermittent contractions are not painful, because the P factor is washed away. Muscle stiffness may be due in part to the accumulation of interstitial fluid in the muscles during exertion.

Heat dissipation during exercise is discussed in Chapter 33 and summarized in Fig 33–4. The changes in acid-base balance associated with respiration are reviewed in Chapter 39.

HYPOXIA

Hypoxia is O_2 deficiency at the tissue level. It is a more correct term than **anoxia**, there rarely being no O_2 at all left in the tissues.

Traditionally, hypoxia has been divided into 4 types. Numerous other classifications have been used, but the four-type system still has considerable utility if the definitions of the terms are kept clearly in mind. The four categories are (1) **hypoxic hypoxia (anoxic anoxia)**, in which the P_{O_2} of the arterial blood is reduced; (2) **anemic hypoxia**, in which the arterial P_{O_2} is normal but the amount of hemoglobin available to carry O_2 is reduced; (3) **stagnant or ischemic hypoxia**, in which the blood flow to a tissue is so low that adequate O_2 is not delivered to it despite a normal P_{O_2} and hemoglobin concentration; and (4) **histotoxic hypoxia**, in which the amount of O_2 delivered to a tissue is adequate but, because of the action of a toxic agent, the tissue cells cannot make use of the O_2 supplied to them.

Effects of Hypoxia

The effects of stagnant hypoxia depend upon the tissue affected. In hypoxic hypoxia and the other generalized forms of hypoxia, the brain is affected first. A sudden drop in the inspired P_{O_2} to less than 20 mm Hg, which occurs, for example, when cabin pressure is suddenly lost in a plane flying above 16,000 m, causes loss of consciousness in about 20 seconds (Fig 37–5) and death in 4–5 minutes. Less severe hypoxia causes a variety of mental aberrations not unlike those produced by alcohol: impaired judgment, drowsiness, dulled pain sensibility, excitement, disorientation,

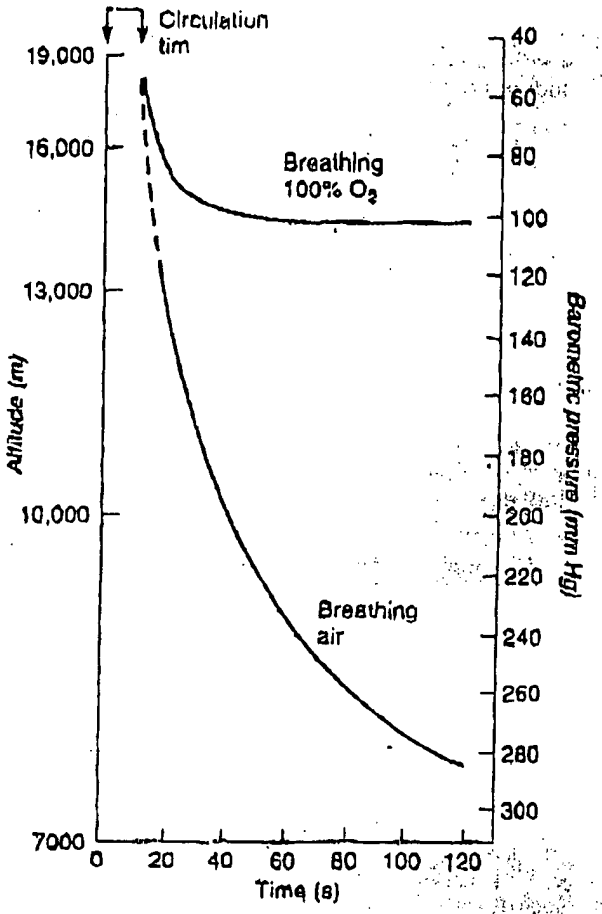


Figure 37–5. Duration of useful consciousness upon sudden exposure to the ambient pressure at various altitudes. Ten seconds is the approximate lung-to-brain circulation time.

loss of time sense, and headache. Other symptoms include anorexia, nausea, vomiting, tachycardia, and, when the hypoxia is severe, hypertension. The rate of ventilation is increased in proportion to the severity of the hypoxia of the carotid chemoreceptor cells.

Respiratory Stimulation

Dyspnea is by definition difficult or labored breathing in which the subject is conscious of shortness of breath; hyperpnea is the general term for an increase in the rate or depth of breathing regardless of the patient's subjective sensations. **Tachypnea** is rapid, shallow breathing. In general, a normal individual is not conscious of respiration until ventilation is doubled, and breathing is not uncomfortable until ventilation is tripled or quadrupled. Whether or not a given level of ventilation is uncomfortable also depends upon the respiratory reserve. Dyspnea is generally present when more than 30% of the respiratory capacity is being used at a given respiratory minute volume. An additional factor is the effort involved in moving the air in and out of the lungs (the work of breathing). In asthma, for example, the bronchi are constricted, especially during expiration, and breathing against this increased airway resistance is uncomfortable work.

Cyanosis

Reduced hemoglobin has a dark color, and a dusky bluish discoloration of the tissues, called **cyanosis**, appears when the reduced hemoglobin concentration of the blood in the capillaries is more than 5 g/dL. Its occurrence depends upon the total amount of hemoglobin in the blood, the degree of hemoglobin unsaturation, and the state of the capillary circulation. Cyanosis is most easily seen in the nail beds and mucous membranes and in the earlobes, lips, and fingers, where the skin is thin. Cyanosis does not occur in anemic hypoxia, because the total hemoglobin content is low; in carbon monoxide poisoning, because the color of reduced hemoglobin is obscured by the cherry-red color of carbonmonoxyhemoglobin (see below); or in histotoxic hypoxia, because the blood gas content is normal. A discoloration of the skin and mucous membranes similar to cyanosis is produced by high circulating levels of methemoglobin (see Chapter 27).

HYPOXIC HYPOXIA

Hypoxic hypoxia is a problem in normal individuals at high altitudes and is a complication of pneumonia and a variety of other diseases of the respiratory system.

Effects of Decreased Barometric Pressure

The composition of air stays the same, but the total barometric pressure falls with increasing altitude (Fig 37–6). Therefore, the P_{O_2} also falls. At 3000 m (approximately 10,000 ft) above sea level, the alveolar P_{O_2} is about 60 mm Hg and there is enough hypoxic stimulation of the chemoreceptors to definitely increase ventilation. As one ascends higher, the alveolar P_{O_2} falls less rapidly and the alveolar P_{CO_2} declines somewhat because of the hyperventilation. The resulting fall in arterial P_{CO_2} produces respiratory alkalosis.

Hypoxic Symptoms Breathing Air

There are a number of compensatory mechanisms that operate over a period of time to increase altitude tolerance (**acclimatization**), but in unacclimatized subjects, mental symptoms such as irritability appear at about 3700 m. At 5500 m, the hypoxic symptoms are severe; and at altitudes above 6100 m (20,000 ft), consciousness is usually lost (Fig 37–7).

Hypoxic Symptoms Breathing Oxygen

The total atmospheric pressure becomes the limiting factor in altitude tolerance when breathing 100%

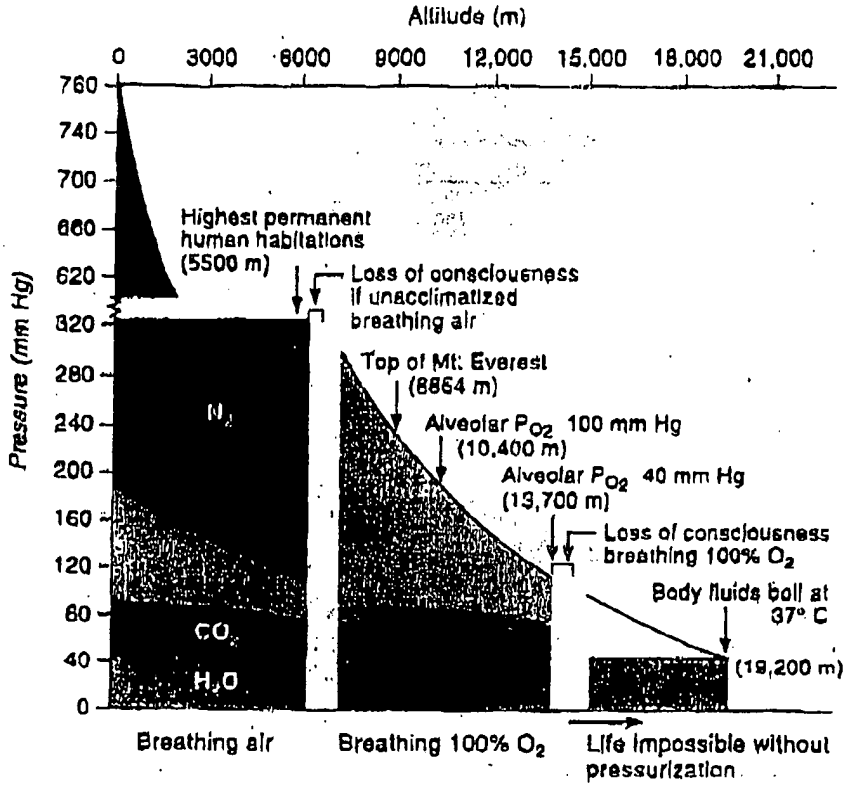


Figure 37–6. Composition of alveolar air in individuals breathing air (0–6100 m) and 100% O_2 (6100–13,700 m). The minimal alveolar P_{O_2} that an unacclimatized subject can tolerate without loss of consciousness is about 35–40 mm Hg. Note that with increasing altitude, the alveolar P_{CO_2} drops because of the hyperventilation due to hypoxic stimulation of the carotid and aortic chemoreceptors. The fall in barometric pressure with increasing altitude is not linear, because air is compressible.

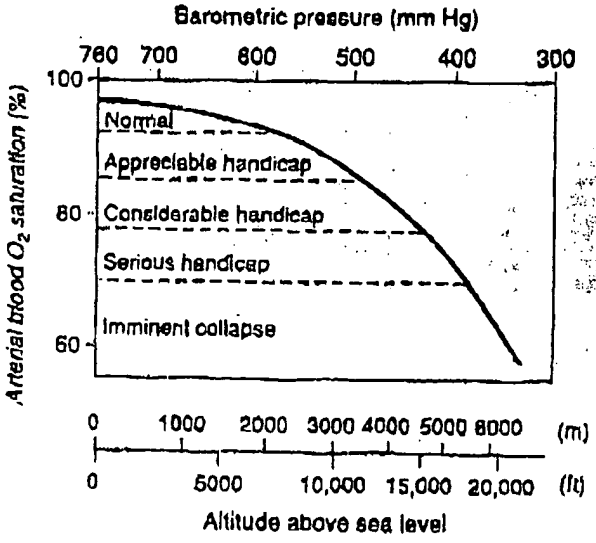


Figure 37–7. Acute effects of hypoxia in individuals breathing air at various altitudes.

O_2. The partial pressure of water vapor in the alveolar air is constant at 47 mm Hg, and that of CO_2 is normally 40 mm Hg, so that the lowest barometric pressure at which a normal alveolar P_{O_2} of 100 mm Hg is possible is 187 mm Hg, the pressure at about 10,400 m (34,000 ft). At greater altitudes, the increased ventilation due to the decline in alveolar P_{O_2} lowers the alveolar P_{CO_2} somewhat, but the maximum alveolar P_{O_2} that can be attained when breathing 100% O_2 at the ambient barometric pressure of 100 mm Hg at 13,700 m is about 40 mm Hg. At about 14,000 m, consciousness is lost in spite of the administration of 100% O_2 (Fig 37–5). However, an artificial atmosphere can be created around an individual; in a pressurized suit or cabin supplied with O_2 and a system to remove CO_2, it is possible to ascend to any altitude and to live in the vacuum of interplanetary space.

At 19,200 m, the barometric pressure is 47 mm Hg, and at or below this pressure the body fluids boil at body temperature. The point is largely academic, however, because any individual exposed to such a low pressure would be dead of hypoxia before the bubbles of steam could cause death.

Delayed Effects of High Altitude

Many individuals, when they first arrive at a high altitude, develop transient "mountain sickness." This syndrome develops 8–24 hours after arrival at altitude and lasts 4–8 days. It is characterized by headache, irritability, insomnia, breathlessness, and nausea and vomiting. Its cause is unsettled, but it appears to be associated with cerebral edema. The low P_{O_2} at high altitude causes arteriolar dilation, and if cerebral autoregulation does not compensate, there is an increase in capillary pressure that favors increased transudation of fluid into brain tissue. Individuals who do not develop mountain sickness have a diuresis at high altitude, and urine volume is decreased in individuals who develop the condition. However, treatment with diuretics does not prevent mountain sickness. The symptoms are reduced if alkalosis is reduced by treatment with acetazolamide or if the cerebral edema is reduced by administration of large doses of glucocorticoids.

High-altitude pulmonary edema and cerebral edema are serious forms of mountain sickness. Pulmonary edema is prone to occur in individuals who ascend quickly to altitudes above 2500 m and engage in heavy physical activity during the first 3 days after arrival. It is also seen in individuals acclimatized to high altitudes who spend 2 weeks or more at sea level and then reascend. It occurs in the absence of cardiovascular or pulmonary disease. It is associated with marked pulmonary hypertension, but left atrial pressures are normal. The edema fluid is of the high-permeability type, with a high content of protein and blood cells. It has been suggested that it occurs because not all pulmonary arteries have enough smooth muscle to constrict in response to hypoxia, and in the capillaries supplied by those arteries, the general rise in pulmonary arterial pressure causes a capillary pressure increase that disrupts their walls (stress failure). In any case, the Ca^{2+} channel-blocking drug nifedipine, which lowers pulmonary arterial pressure, is of value in the treatment and prevention of the condition. Pulmonary edema also responds to rest and O_2 treatment and generally does not develop in individuals who ascend to high altitudes gradually and avoid physical exertion for the first few days of high-altitude exposure.

Acclimatization

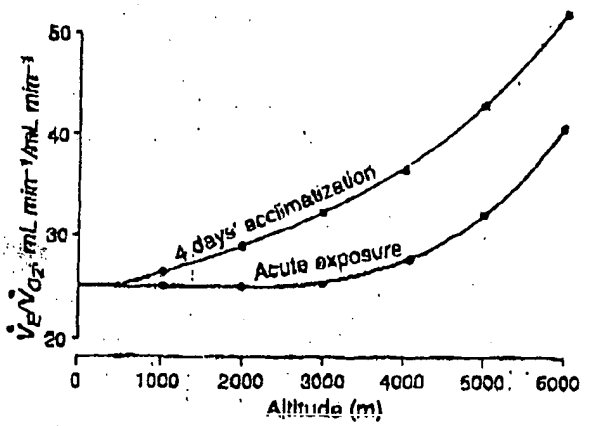
Acclimatization to altitude is due to the operation of a variety of compensatory mechanisms. The respiratory alkalosis produced by the hyperventilation shifts the oxygen-hemoglobin dissociation curve to the left, but there is a concomitant increase in red blood cell 2,3-DPG, which tends to decrease the O_2 affinity of hemoglobin. The net effect is a small increase in P_{50} (see Chapter 35). The decrease in O_2 affinity makes more O_2 available to the tissues. However, the value of the increase in P_{50} is limited because when the arterial P_{O_2} is markedly reduced, the decreased O_2 affinity also interferes with O_2 uptake by hemoglobin in the lungs.

The initial ventilatory response to increased altitude is relatively small, because the alkalosis tends to counteract the stimulating effect of hypoxia. However, there is a steady increase in ventilation over the next 4 days (Fig 37–8) because the active transport of H^+ into CSF, or possibly a developing lactic acidosis in the brain, causes a fall in CSF pH that increases the response to hypoxia. After 4 days, the ventilatory response begins to decline slowly, but it takes years of residence at higher altitudes for it to decline to the initial level. Associated with this decline is a gradual desensitization to the stimulatory effects of hypoxia.

Erythropoietin secretion increases promptly on ascent to high altitude (see Chapter 24) and then falls somewhat over the following 4 days as the ventilatory response increases and the arterial P_{O_2} rises. The increase in circulating red blood cells triggered by the erythropoietin begins in 2–3 days and is sustained as long as the individual remains at high altitude.

There are also compensatory changes in the tissues. The mitochondria, which are the site of oxidative reactions, increase in number, and there is an increase in myoglobin (see Chapter 35) that facilitates the movement of O_2 in the tissues. There is also an increase in the tissue content of cytochrome oxidase.

The effectiveness of the acclimatization process is indicated by the fact that in the Andes and Himalayas there are permanent human habitations at elevations above 5500 m (18,000 ft). The natives who live in these villages are barrel-chested and markedly polycythemic. They have low alveolar P_{O_2} values, but in most other ways they are remarkably normal.



Figur 37–8. Effect of acclimatization on the ventilatory response at various altitudes. $\dot{V}_E/\dot{V}_{O_2}$ is the ventilatory equivalent, the ratio of expired minute volume ($\dot{V}_E$) to the O_2 consumption ($\dot{V}_{O_2}$). (Reproduced, with permission, from Lenfant C, Sullivan K: Adaptation to high altitude. *N Engl J Med* 1971;284:1298.)

Diseases Causing Hypoxic Hypoxia

Hypoxic hypoxia is the most common form of hypoxia seen clinically. The diseases that cause it can be roughly divided into those in which the gas exchange apparatus fails, those such as congenital heart disease in which large amounts of blood are shunted from the venous to the arterial side of the circulation, and those in which the respiratory pump fails (Table 37–1). Lung failure occurs when conditions such as pulmonary fibrosis produce alveolar-capillary block or there is ventilation-perfusion imbalance. Pump failure can be due to fatigue of the respiratory muscles in conditions in which the work of breathing is increased or to a variety of mechanical defects such as pneumothorax or bronchial obstruction that limit ventilation. It can also be caused by abnormalities of the neural mechanisms that control ventilation, such as depression of the respiratory neurons in the medulla by morphine and other drugs.

Ventilation-Perfusion Imbalance

Patchy ventilation-perfusion imbalance is by far the most common cause of hypoxic hypoxia in clinical situations. The physiologic effects of ventilation-perfusion imbalance and their role in producing the alterations in alveolar gas due to gravity are discussed in Chapter 34.

In disease processes that prevent ventilation of some of the alveoli, the ventilation-blood flow ratios in different parts of the lung determine the extent to which systemic arterial P_{O_2} declines. If nonventilated alveoli are perfused, the nonventilated but perfused portion of the lung is in effect a right-to-left shunt, dumping unoxygenated blood into the left side of the heart. Lesser degrees of ventilation-perfusion imbalance are more common. In the example illustrated in Fig 37–9, the underventilated alveoli (B) have a low alveolar P_{O_2}, whereas the overventilated alveoli (A) have a high alveolar P_{O_2}. However, the unsaturation of the hemoglobin of the blood coming from B is not completely compensated by the greater saturation of the blood coming from A, because hemoglobin is normally nearly saturated in the lungs and the higher alveolar P_{O_2} adds only a little more O_2 to the hemoglobin than it normally carries. Consequently, the arterial blood is unsaturated. On the other hand, the CO_2 content of the arterial blood is generally normal in such situations, since extra loss of CO_2 in overventilated regions can balance diminished loss in underventilated areas.

Table 37–1. Disorders causing hypoxic hypoxia.

Lung failure (gas exchange failure)
Pulmonary fibrosis
Ventilation-perfusion imbalance
Shunt
Pump failure (ventilatory failure)
Fatigue
Mechanical defects
Depression of respiratory controller in the brain

Venous-to-Arterial Shunts

When a cardiovascular abnormality such as an interatrial septal defect permits large amounts of unoxygenated venous blood to bypass the pulmonary capillaries and dilute the oxygenated blood in the systemic arteries ("right-to-left shunt"), chronic hypoxic hypoxia and cyanosis (**cyanotic congenital heart disease**) result. Administration of 100% O_2 raises the O_2 content of alveolar air and improves the hypoxia due to hypoventilation, impaired diffusion, or ventilation-perfusion imbalance (short of perfusion of totally unventilated segments) by increasing the amount of O_2 in the blood leaving the lungs. However, in patients with venous-to-arterial shunts and normal lungs, any beneficial effect of 100% O_2 is slight and is due solely to an increase in the amount of dissolved O_2 in the blood.

Collapse of the Lung

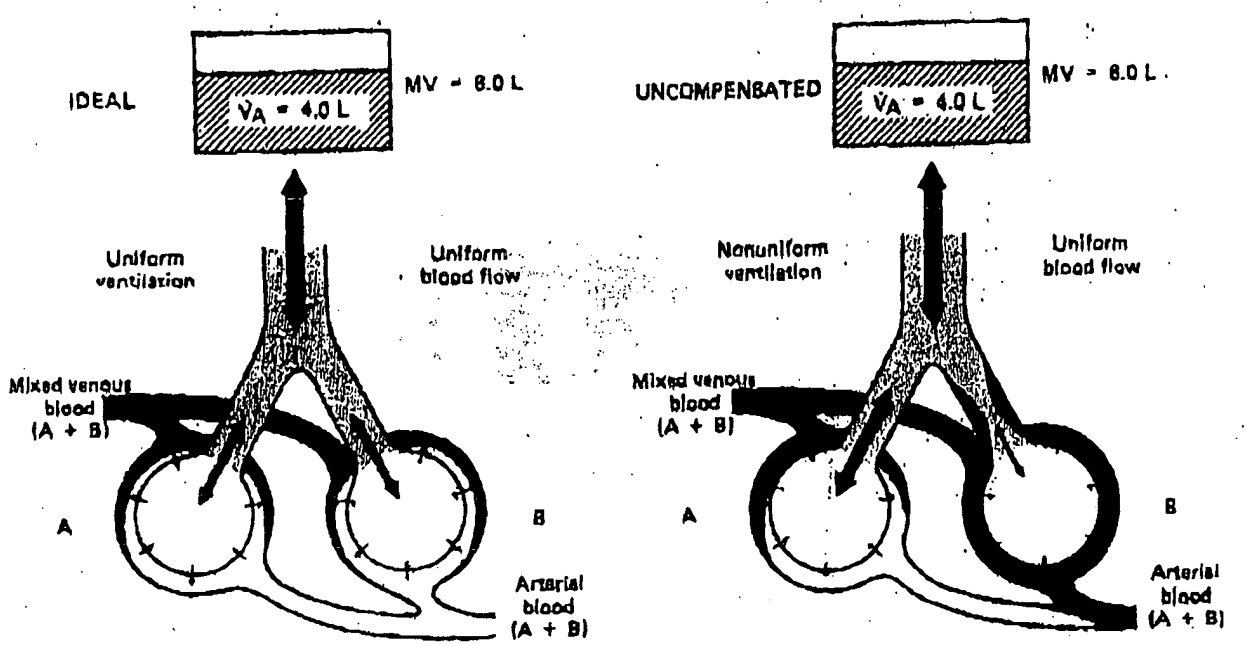
When a bronchus or bronchiole is obstructed, the gas in the alveoli beyond the obstruction is absorbed and the lung segment collapses. Collapse of alveoli is called **atelectasis**. The atelectatic area may range in size from a small patch to a whole lung. Some blood is diverted from the collapsed area to better ventilated portions of the lung, and this reduces the magnitude of the decline in arterial P_{O_2}.

When a large part of the lung is collapsed, there is an appreciable decrease in lung volume. The intrapleural pressure therefore becomes more negative and pulls the mediastinum, which in humans is a fairly flexible structure, to the affected side.

Another cause of atelectasis is absence or inactivation of surfactant, the surface-tension-depressing agent normally found in the thin fluid lining the alveoli (see Chapter 34). This abnormality is a major cause of failure of the lungs to expand normally at birth. Collapse of the lung may also be due to the presence in the pleural space of air (**pneumothorax**), tissue fluids (**hydrothorax, chylothorax**), or blood (**hemothorax**).

Pneumothorax

When air is admitted to the pleural space, through either a rupture in the lung or a hole in the chest wall, the lung on the affected side collapses because of its elastic recoil. Since the intrapleural pressure on the affected side is now atmospheric, the mediastinum shifts toward the normal side. If the communication between the pleural space and the exterior remains open (**open or sucking pneumothorax**), more air moves in and out of the pleural space each time the patient breathes. If the hole is large, the resistance to air flow into the pleural cavity is less than the resistance to air flow into the intact lung, and little air enters the lung. During inspiration, the mediastinum



	A	B	A+B
Alveolar ventilation (L/min)	2.0	2.0	4.0
Pulmonary blood flow (L/min)	2.5	2.5	5.0
Ventilation/blood flow ratio	0.8	0.8	0.8
Mixed venous O_2 saturation (%)	75.0	75.0	75.0
Arterial O_2 saturation (%)	97.4	97.4	97.4
Mixed venous O_2 tension (mm Hg)	40.0	40.0	40.0
Alveolar O_2 tension (mm Hg)	104.0	104.0	104.0
Arterial O_2 tension (mm Hg)	104.0	104.0	104.0

	A	B	A+B
Alveolar ventilation (L/min)	3.2	0.8	4.0
Pulmonary blood flow (L/min)	2.5	2.5	5.0
Ventilation/blood flow ratio	1.3	0.3	0.8
Mixed venous O_2 saturation (%)	75.0	75.0	75.0
Arterial O_2 saturation (%)	98.2	81.7	95.0
Mixed venous O_2 tension (mm Hg)	40.0	40.0	40.0
Alveolar O_2 tension (mm Hg)	116.0	66.0	108.0
Arterial O_2 tension (mm Hg)	116.0	66.0	84.0

Figure 37–9. ***Left:*** "Ideal" ventilation/blood flow relationship. ***Right:*** Nonuniform ventilation and uniform blood flow, uncompensated. $\dot{V}_A$, alveolar ventilation; MV, respiratory minute volume. (Reproduced, with permission, from Comroe JH Jr et al: *The Lung: Clinical Physiology and Pulmonary Function Tests*, 2nd ed. Year Book, 1962.)

shifts farther to the intact side, kinking the great vessels until it flaps back during expiration. There is marked stimulation of respiration due to hypoxia, hypercapnia, and activation of pulmonary deflation receptors. Respiratory distress is severe.

If there is a flap of tissue over the hole in the lung or chest wall that acts as a flutter valve, permitting air to enter during inspiration but preventing its exit during expiration, the pressure in the pleural space rises above atmospheric pressure (**tension pneumothorax**). The hypoxic stimulus to respiration causes deeper inspiratory efforts, which further increase the pressure in the pleural cavity, kinking the great veins and causing further hypoxia and shock. Intrapleural pressure in such cases may rise to 20–30 mm Hg. The peripheral veins become distended, there is intense cyanosis, and the condition is potentially fatal if the pneumothorax is not decompressed by removing the air.

On the other hand, if the hole through which air enters the pleural space seals off (**closed pneumothorax**), respiratory distress is not great because, with each inspiration, air flows into the lung on the unaffected side rather than into the pleural space. Because the vascular resistance is increased in the collapsed lung, blood is diverted to the other lung. Consequently, unless the pneumothorax is very large, it does not cause much hypoxia.

The air in a closed pneumothorax is absorbed. Since it is at atmospheric pressure, its total pressure, P_{O_2}, and P_{N_2} are greater than the corresponding values in venous blood (compare values for air and venous blood in Fig 34–15). Gas diffuses down these gradients into the blood, and after 1–2 weeks all of the gas disappears.

Asthma

Asthma is characterized by episodic or chronic wheezing, cough, and a feeling of tightness in the chest as a result of bronchoconstriction. Its morbidity and mortality are increasing, and its fundamental cause is still unknown despite intensive research. However, three abnormalities are present: airway obstruction that is at least partially reversible, airway inflammation, and airway hyperresponsiveness to a variety of stimuli. A link to allergy has long been recognized, and plasma IgE levels are often elevated.

Proteins released from eosinophils in the inflammatory reaction may damage the airway epithelium and contribute to the hyperresponsiveness. Leukotrienes are released from eosinophils and mast cells, and leukotrienes cause bronchoconstriction. Other bronchoconstrictors that may be involved include endothelin-1, and there is some evidence for a deficiency of VIP, a bronchodilator. Asthma attacks are more severe in the late-night and early-morning hours because, as noted above, this is the period of maximal constriction in the circadian rhythm of bronchial tone. Cool air and exercise, both of which normally cause bronchoconstriction, also trigger asthma attacks, and the effects of both are inhibited by inhibitors of leukotriene synthesis or action. β-Adrenergic receptors mediate bronchodilation, and treatment with inhaled β-adrenergic agonists is a standard therapy for asthma. Muscarinic receptors mediate bronchoconstriction, and muscarinic cholinergic blocking drugs are also used for treatment. Additional drugs that are commonly used are cromolyn, which inhibits release of mast cell products, and glucocorticoids, which inhibit the inflammatory response.

Emphysema

In the degenerative and potentially fatal pulmonary disease called **emphysema**, the lungs lose their elasticity as a result of disruption of elastic tissue and the walls between the alveoli break down so that the alveoli are replaced by large air sacs. The physiologic dead space is greatly increased, and because of inadequate and uneven alveolar ventilation and perfusion of underventilated alveoli, severe hypoxia develops. Late in the disease, hypercapnia also develops. Inspiration and expiration are labored, and the work of breathing is greatly increased. The changes in the pressure-volume curve of the lungs are shown in Fig 34–8. The chest becomes enlarged and barrel-shaped because the chest wall expands as the opposing elastic recoil of the lungs declines. The hypoxia leads to polycythemia. Pulmonary hypertension develops, and the right side of the heart enlarges (**cor pulmonale**) and then fails.

The most common cause of emphysema is heavy cigarette smoking. The smoke causes an increase in the number of pulmonary alveolar macrophages, and these macrophages release a chemical substance that attracts leukocytes to the lungs. The leukocytes in turn release proteases including elastase, which attacks the elastic tissue in the lungs. At the same time, α_1-antitrypsin, a plasma protein that normally inactivates elastase and other proteases, is itself inhibited. The α_1-antitrypsin is inactivated by oxygen radicals, and these are released by the leukocytes. The final result is a protease-antiprotease imbalance with increased destruction of lung tissue.

In about 2% of cases of emphysema, there is a congenital deficiency of active α_1-antitrypsin. If individuals who are homozygous for this deficiency smoke, they develop crippling emphysema early in life and have a 20-year reduction in their life span. If they do not smoke, they may still develop emphysema, but they do much better and their life expectancy is much improved. Thus, α_1-antitrypsin deficiency provides an interesting example of the interaction between genetic factors and environmental factors in the production of disease.

Cystic Fibrosis

Cystic fibrosis is another condition that leads to repeated pulmonary infections and progressive, eventually fatal destruction of the lungs. In this congenital recessive disorder, a Cl^- channel in the apical membrane of airway epithelial cells is not activated in a normal fashion by cyclic AMP. An additional Cl^- channel in the membrane is normal but may have its function depressed. In any case, loss of the cyclic AMP-activated channel results in a decrease in the transport of Cl^- into the airways. Na^+ and H_2O are reabsorbed from the airways at an increased rate, and the decrease in Na^+ and H_2O content makes the mucus that they contain thick and inspissated. Among Caucasians, cystic fibrosis is one of the most common genetic disorders: 5% of the population carry a defective gene, and the disease occurs in one of every 2000 births.

The gene that is abnormal in cystic fibrosis is located on the long arm of chromosome 7 and encodes a Cl^- channel called the **cystic fibrosis transmembrane conductance regulator (CFTR)**, which has 12 membrane-spanning domains, two ATP-binding sites, and a region containing phosphorylation sites for cyclic AMP-dependent protein kinase (protein kinase A) (see Chapter 1). This channel is a member of a superfamily of transporters that mediate, among other things, export of the α-factor mating pheromone in yeast and probably secretion of proteins lacking a signal sequence in mammals. The number of reported mutations in the *CFTR* gene that cause cystic fibrosis has now passed 24, and the severity of the defect varies with the mutation, but this is not surprising in a gene encoding such a complex protein. In most cases, the mutations interfere with ATP-binding or the conformational change that is presumably produced by the binding.

OTHER FORMS OF HYPOXIA

Anemic Hypoxia

Hypoxia due to anemia is not severe at rest unless the hemoglobin deficiency is marked, because red blood cell 2,3-DPG increases. However, anemic patients may have considerable difficulty during exercise because of limited ability to increase O_2 delivery to the active tissues (Fig 37–10).

Carbon Monoxide Poisoning

Small amounts of carbon monoxide (CO) are formed in the body, and this gas may function as a

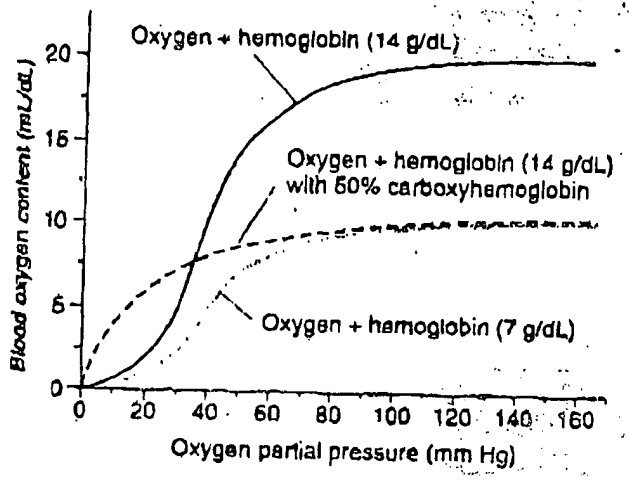


Figure 37–10. Normal oxyhemoglobin dissociation curve (top; hemoglobin concentration, 14g/dL) compared to oxyhemoglobin dissociation curves in CO poisoning (50% carboxyhemoglobin) and anemia (hemoglobin concentration, 7 g/dL). Note that the CO-poisoning curve is shifted to the left of the anemia curve. (Reproduced, with permission from Lefl AR, Schumacker PT: *Respiratory Physiology. Basics and Applications.* Saunders, 1993.)

chemical messenger in the brain and elsewhere (see Chapters 4 and 27). In larger amounts, it is poisonous. Outside the body, it is formed by incomplete combustion of carbon. It was used by the Greeks and Romans to execute criminals, and today it causes more deaths than any other gas. CO poisoning has become less common in the United States, since natural gas, which does not contain CO, replaced artificial gases such as coal gas, which contains large amounts. However, the exhaust of gasoline engines is 6% or more CO.

CO is toxic because it reacts with hemoglobin to form **carbonmonoxyhemoglobin (carboxyhemoglobin, COHb)**, and COHb cannot take up O_2 (Fig 37–10). Carbon monoxide poisoning is often listed as a form of anemic hypoxia because there is a deficiency of hemoglobin that can carry O_2, but the total hemoglobin content of the blood is unaffected by CO. The affinity of hemoglobin for CO is 210 times its affinity for O_2, and COHb liberates CO very slowly. An additional difficulty is that when COHb is present the dissociation curve of the remaining HbO_2 shifts to the left, decreasing the amount of O_2 released. This is why an anemic individual who has 50% of the normal amount of HbO_2 may be able to perform moderate work, whereas an individual whose HbO_2 is reduced to the same level because of the formation of COHb is seriously incapacitated.

Because of the affinity of CO for hemoglobin, there is progressive COHb formation when the alveolar P_{CO} is greater than 0.4 mm Hg. However, the amount of COHb formed depends upon the duration of exposure to CO as well as the concentration of CO in the inspired air and the alveolar ventilation.

CO is also toxic to the cytochromes in the tissues, but the amount of CO required to poison the cytochromes is 1000 times the lethal dose; tissue toxicity thus plays no role in clinical CO poisoning.

The symptoms of CO poisoning are those of any type of hypoxia, especially headache and nausea, but there is little stimulation of respiration, since in the arterial blood, P_{O_2} remains normal and the carotid and aortic chemoreceptors are not stimulated (see Chapter 36). The cherry-red color of COHb is visible in the skin, nail beds, and mucous membranes. Death results when about 70–80% of the circulating hemoglobin is converted to COHb. The symptoms produced by chronic exposure to sublethal concentrations of CO are those of progressive brain damage, including mental changes and, sometimes, a parkinsonismlike state (see Chapter 32).

Treatment of CO poisoning consists of immediate termination of the exposure and adequate ventilation, by artificial respiration if necessary. Ventilation with O_2 is preferable to ventilation with fresh air, since O_2 hastens the dissociation of COHb. Hyperbaric oxygenation (see below) is useful in this condition.

Stagnant Hypoxia

Hypoxia due to slow circulation is a problem in organs such as the kidneys and heart during shock (see Chapter 33). The liver and possibly the brain are damaged by stagnant hypoxia in congestive heart failure. The blood flow to the lung is normally very large, and it takes prolonged hypotension to produce significant damage. However, ARDS (see Chapter 33) can develop when there is prolonged circulatory collapse.

Histotoxic Hypoxia

Hypoxia due to inhibition of tissue oxidative processes is most commonly the result of cyanide poisoning. Cyanide inhibits cytochrome oxidase and possibly other enzymes. Methylene blue or nitrites are used to treat cyanide poisoning. They act by forming **methemoglobin**, which then reacts with cyanide to form **cyanmethemoglobin**, a nontoxic compound. The extent of treatment with these compounds is, of course, limited by the amount of methemoglobin that can be safely formed. Hyperbaric oxygenation may also be useful.

OXYGEN TREATMENT

Value

Administration of oxygen-rich gas mixtures is of very limited value in stagnant, anemic, and histotoxic hypoxia because all that can be accomplished in this way is an increase in the amount of dissolved O_2 in the arterial blood. This is also true in hypoxic hypoxia when it is due to shunting of unoxygenated venous blood past the lungs. In other forms of hypoxic hypoxia, O_2 is of great benefit. Treatment regimes that de-